

PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

AN, J. et al.

APPLICATION NO.: 10/588,883

FILED: 8 MAY 2007

FOR: **METHODS FOR ISOLATION OF TRIPTOLIDE
COMPOUNDS FROM TRIPTRYGIUM
WILFORDII**

EXAMINER: MABRY, JOHN

ART UNIT: 1625

CONF. NO: 4457

Pre-Appeal Brief Request for Review

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Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants have considered the Final Office Action mailed 19 January 2011 in the above-identified application. Reconsideration of the claims in light of the remarks that follow is respectfully requested.

A Notice of Appeal is being filed with this request.

Remarks begin on page 2 of this paper.

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REMARKS**I. Status of the Claims**

Claims 1-17 are pending and under consideration. No claim is allowed.

II. Rejection under 35 U.S.C. §103

The sole issue outstanding in the pending application is whether claims 1-17 under 35 U.S.C. §103(a) are obvious over US Patent No. 5,430,054 to Qian *et al.* (hereinafter "US '054") in view of US Patent No. 5,192,817 to Takaishi *et al.* (hereinafter "US '817") and in further view of Beroza 1953 and Beroza 1952 (JACS 1953, 75, 44-49 and JACS 1952, 74, 1585-1588). Applicants have traversed, and the Examiner has maintained the rejection.

A. The Present Claims

Independent claim 1 is directed to a method for purifying an extract of *Tripterygium wilfordii* plant material containing triptolide¹ and related compounds, wherein the extract is formed by (a) extracting plant material with aqueous ethanol, and concentrating to obtain a residue; and (b) forming a slurry of this residue in chlorinated organic solvent; partitioning the slurry with water for a period of about 10 mins-10 hours; and then removing the water; wherein purifying comprises the steps of: (c) further partitioning the slurry with an aqueous solution of base, removing the aqueous solution of base, and removing at least a portion of the organic solvent from the slurry; (d) washing the product of step (c) with a lipophilic solvent; and (e) eluting the washed product from step (d) from a silica gel adsorbent.

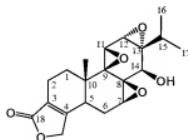
B. The Cited Art

US '054 describes methods of preparation of diterpene lactone compounds from extracts of leaves of *Tripterygium* plants, and the use of these compounds as anti-fertility agents.

US '817 describes phenanthrene derivatives and a method of extracting *Tripterygium Wilfordii* Hook fil. var. *Regelii* Makino with a polar solvent, concentrating that extract under reduced pressure to obtain a primary extract, and then collecting an intended compound from the primary extract using various methods based on the intended compound's properties.

BEROZA 1953 AND 1952 describe a process for removing alkaloids from the initial extracts of *Tripterygium Wilfordii*.

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C. Analysis

The basis for the present Pre-Appeal Brief Request for Review is that the Examiner has made a legal error in failing to consider Applicants' evidence of unexpected results.

The Examiner acknowledges that the cited art differs from the present claims in that the present claims add a step of further partitioning the slurry with an aqueous solution of base. However, the Examiner alleges that Applicants' base treatment step is obvious, asserting that the '054 and '817 patents teach that initial organic extracts of *Tripterygium wilfordii* contain many acidic compounds, and that Beroza teaches that isolated alkaloids "can be selectively removed by saponified [sic] by using aqueous sodium hydroxide." (Office Action at page 5). The Examiner characterizes Applicants' added step of further partitioning the slurry with an aqueous solution of base as "routine optimization," citing *In re Mostovych*, Weber, Mitchell and Aulbach (144 USPQ 38). (See Office Action at page 6). Further, the Examiner notes:

(t)he claimed step of extraction can be carried out by **multiple extractions of ethanol and plant material followed by pooling of the extracts** (see Summary of the Invention and Description of the Invention, columns 1-2 of US '054).

(Office Action at page 6; emphasis added here).

In Applicants' previous response mailed 8 November 2010, Applicants clearly noted that the state of the art in the field of isolating native compounds from plant material typically required laborious extraction and purification procedures, citing to Applicants' own PCT Publication WO 2005/077008 at page 2, lines 5-6. With that response, Applicants also submitted Exhibits A-C as evidence of knowledge available to skilled artisans at the time of filing that the art taught away from a base treatment step. The Exhibits were:

- A) J. March, (1992) John Wiley & Sons, New York, NY, USA, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," 4th ed., 376-377;
- B) Francis Carey and Richard J. Sundberg, (1983) Plenum Press, New York, "Advanced Organic Chemistry" 2nd ed., Part B: Reactions and Synthesis, 498-499; and
- C) Chen *et al.* *Journal of Controlled Release* 98 (2004) 427–436.

Applicants clearly explained that the skilled artisan's expectation at the time of filing was that basic conditions would hydrolyze and open epoxide rings, and that the expectation was that base treatment of the extract of the present claims would make it impossible to recover triptolide and its related compounds intact, without significant degradation. Exhibits A-C each clearly show that it was well known to skilled artisans that epoxide rings were labile to base treatment. For example, in the March reference from 1992, it states "**Epoxide ring opening reactions are catalyzed by acids or bases and is a convenient method for the preparation of vic-diols.**" (March *Advanced Organic Chemistry*, 4th Ed.; Wiley, 1992, p 376 - 377; emphasis added here). Page 432 of the publication by Chen *et al.* (*Journal of Controlled Release* 98 (2004) 427–436) states:

A long-term storage of triptolide in an aqueous environment may result in a potential tendency of hydrolysis, because triptolide has unstable ether-bond. Therefore, it is disadvantageous that triptolide was formulated to an aqueous environment. The rate of hydrolysis of triptolide is also influenced significantly by pH value. Especially when pH value is less than 3 or more than 8, the hydrolysis of triptolide can be promoted.

(For an illustration of epoxide-opening in NaOH, see Fig. 5 of U.S. Pat. No. 6,150,539 - reference 11 in the IDS submitted 4 December 2006). Applicants clearly explained the proffered evidence, noting that at the time of filing of the present application, the art taught away from the use of base if the skilled artisan's goal was isolation of an epoxide-containing compound. In Applicants' method, the slurry obtained from the extract, as set forth in steps (a) and (b), is partitioned by treatment with aqueous base. The partitioning step is followed by removal of aqueous base, removal of at least a portion of the remaining chlorinated organic solvent, a lipophilic solvent wash, and elution of the isolated material from silica gel. Applicants found that, rather than base-catalyzed hydrolysis of the epoxides, the base treatment step achieves the unexpected effect of increasing efficiency of the preparation of an extract of *Tripterygium wilfordii* (Tw) plant material containing triptolide and related compounds. Base treatment was found *not* to open the epoxide rings, and was further found to rid the extract of significant amounts of impurities, reducing the need for laborious and costly additional treatments, e.g., the "multiple extractions of ethanol and plant material followed by pooling of the extracts" (cited by the Examiner as taught by the US '054 patent). Base treatment did not reduce the extractable amount of triptolide recovered from Tw tissues, but in fact the recovery of triptolide was increased over separation methods absent a base-treatment step. Thus, treatment with base was not only surprising with respect to the lack of base-catalyzed epoxide ring opening, but also solved several other processing problems – increasing product yield, reducing the number of purification steps required, circumventing having to deal with removal of oily impurities, and reducing processing costs. Unexpectedly, recovery of triptolide and related compounds was found to be enhanced by Applicants' method over traditional separation approaches. Because the percentage of crude extract containing the desired triptolide and related compounds is increased and isolation steps are eliminated, production costs are reduced and the final yield of triptolide and related compounds is increased. These features of the method were utterly unexpected.

In the Final Office Action at page 9, the Examiner critiques Applicants' submission of Exhibits A-C, stating:

Applicant has not submitted the "unpredictable results" in the form of an affidavit or declaration. The proper and acceptable way of submitting unpredictable results would be by way of a properly filed affidavit or declaration.

The Examiner then goes on to say that "(e)ven though Applicant has not properly submitted the unpredictable results in proper form, Examiner will address Applicant's remarks."

Applicants are not required to submit evidence of unexpected results in the form of a declaration, and respectfully call the Reviewers' attention to M.P.E.P. 716.02(g), which notes that publications may be evidence of the facts at issue and should be considered to the extent that they are probative.

Rather than address Applicants' evidence, the Examiner's rebuttal merely reiterates the rejection, stating:

Although the literature in the art may teach away from the use of a base, Examiner provided motivation for the use of a base in accordance with the claimed invention.

No other reasoning is provided to refute Applicants' evidence of unexpected results. The Examiner clearly failed to consider the state of the art at the time of filing and Applicants' probative evidence of the facts at issue.

For the Examiner to call the addition of the step of further partitioning the slurry with an aqueous solution of base with "routine optimization" is to use hindsight recognition, selecting teachings in the art about saponification and the use of base for isolation of other compounds from plant extracts, while ignoring the evidence provided by applicant of the teachings in the art away from the use of base for treatment of epoxy-containing compounds.

In view of the foregoing, claims 1-17 are believed to satisfy all of the criteria for patentability and are in condition for Allowance. Applicants urge the Reviewers to consider the evidence of unexpected results and come to the same conclusion.

No fees are believed to be due in connection with this response. However, the Commissioner is authorized to charge any additional fees that may be required, or credit any overpayment, to King & Spalding LLP Deposit Account No. 50-4616.

Respectfully submitted,
KING & SPALDING LLP

Date: 1 April 2011

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